The Computational Toxicology Program in ORD

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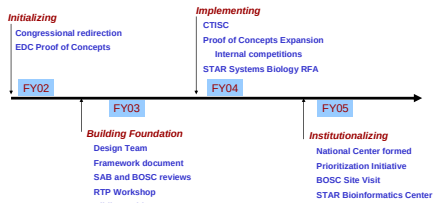
The U.S. Environmental Protection Agency (U.S. EPA) is facing increasingly greater demands to develop more efficient and effective methods to evaluate the hazards and risks of chemicals to human health and the environment. To address this need, the ORD has launched a new research program titled Computational Toxicology. Computational Toxicology is defined in the "Framework for a Computational Toxicology Research Program" (see www.epa.gov/comptox) as the application of mathematical and computer models and molecular biological approaches to improve the Agency's prioritization of data requirements and risk assessments. The program traces its origins to a Congressional reprogramming action in FY02, which directed the Agency to conduct research to explore the use of alternatives to animals in testing. In response to that, several proof-of-concept studies for endocrine disruption were undertaken, as it was felt that the U.S. EPA already had a strong research presence in the area and that considerable information was known about the relevant toxicity pathways. Over the past several years, the program has grown in size and importance. This year, the ORD institutionalized the effort by creating the National Center for Computational Toxicology at its campus in Research Triangle Park, NC. The Center is being staffed with systems biologists, computational chemists, and bioinformaticians and will be the focal point for computational toxicology efforts across the ORD. One of the main early challenges of the program will be to develop approaches for prioritizing chemical lists of concern to the Agency for screening and testing purposes. Ideally, this will lead to tailored testing schemes for environmental stressors and to the more effective and efficient use of animals in research. This, in turn, will lead to improved risk assessment methodologies and outcomes. A key part of the program will be development of partnerships with outside organizations that we facilitate and the ensuing discussion of key research needs.

Program Development



ORD's Computational Toxicology Research Program

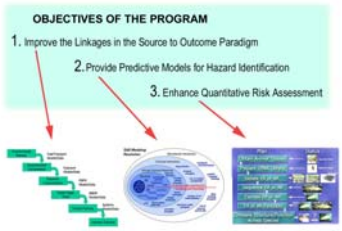
Themes:

- A technology-based, hypothesis-driven effort to increase the soundness of risk assessment decisions within EPA
- Build the capacity to prioritize, screen and evaluate chemicals by enhancing the predictive understanding of toxicity pathways

Success:

- Measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern

www.epa.gov/comptox



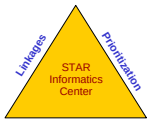
ORD Workshop, 9/03

- Introduction to the Framework
- Related research strategies from other organizations
- Highlighted approaches
  - Diagnostic indicators, high throughput screening, toxicity pathway identification, metabonomics and systems biology
- Regulatory needs
  - OPPTS, OPP, FDA
- Breakout group discussions
  - "top down" and "bottom up"

PoCs, *Augmentations* & New Starts

Amphibian Systems Model
Fish Proteomics
Fish Toxicogenomics
Fish metabonomics
Conazole MOA
Children's Health
Pulmonary Biomarkers
Microbial Metagenomics
STAR Systems Models

DSSTox
Metabolic Simulator
ASTER
ER Binding Data
Molecular Docking
ER/AR Scale up
H295R Assay
Iconix Contract
STAR HTPS RFA

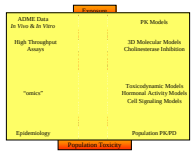


QRA
Diesel Particles
HPG Axis Modal
Pellston, SOT and NCEA Workshops

Denotes Center Staff Participation

Through the actions of a cross EPA working group (the CTISC), a number of projects supporting the Framework were initiated in the past year. Details of each effort are available on the CompTox website.

Systems Biology Modeling

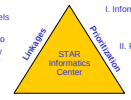


Emerging Focal Areas for the NCCT

II. Biological Models
H Barton
J Blancato
R Conolly
W Setzer
M Zager

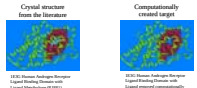
I. Information Technology
A Richard

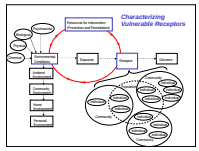
II. Prioritization and Screening
J Rabinowitz
R Kavlock

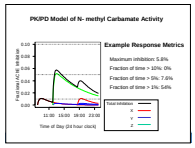


QRA
IV. Cumulative Risk
E Hubal
W Setzer

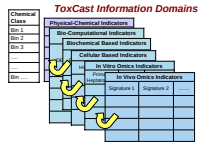
Docking





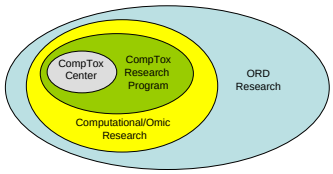


ToxCast Information Domains



NCCT Mission

- To provide **scientific expertise and leadership** related to the application of mathematical and computational tools and models
- To **improve the predictive capabilities** of the methods, models and measurements that constitute the input materials to the computational models.
- To **conduct and/or sponsor research** to provide models for fate and transport of chemicals, environmental exposures to humans and wildlife, delivery of the chemical to the target site of toxicity, molecular and cellular pathways of toxicity, and ultimately systems level understanding of biological processes and their perturbation
- Maintain a strong emphasis on the **development of partnerships** with other government and private organizations



The systems biologists, computational chemists and bioinformaticians within the NCCT will be serving a catalyst to introduce new technologies for prioritization of chemicals for testing and in assessment of risk

Partnerships

- Department of Energy
- Department of Defense
- NIEHS
- NCTR
- IBM
- Affymetrix
- CIIT Centers for Health Research
- ITSC (Former Soviet Union)
- SBIR Solicitation
  - Released March 24 2005; closes May 25 2005
  - Exposure diagnostics, biotransformations, docking models, QSAR databases and models, molecular signatures, omic integration